

REMARKS/ARGUMENTS

Claims 1 and 7-25 are active. Claims 22 and 23 have been revised for clarity. No new matter has been introduced. The Applicants respectfully request that this after-final Amendment be entered by the Examiner to place this application in condition for allowance or in better condition for appeal. The proposed amendments do not raise new issues or necessitate a new search by the Examiner, since the amendment is based on elements earlier claimed or inherent in the previously examined claims. Entry of this Amendment would also permit the Applicants to respond to new arguments raised in the final rejection.

Provisional Obviousness-type Double Patenting

Claims 21-25 were provisionally rejected under the judicially-created doctrine of obviousness type double patenting over claims 1-3, 6, 7, 12 and 13 of copending U.S. Application No. 11/847,593. PAIR shows the status of copending U.S. Application 11/847,593 as "Notice of Allowance Mailed" as of March 26, 2010. However, claims 1-3, 6, 7, 12 and 13 upon which this provisional rejection is based were cancelled prior to allowance. Consequently, this rejection cannot be sustained.

Obviousness-type Double Patenting

Claims 1 and 7-25 were rejected under the judicially-created doctrine of obviousness type double patenting over claims 1-4, 6, 10-13, 15, 21-23, 26, 27, and 29-32 of U.S. Patent No. 7,071,189, in view of copending U.S. Application No. 11/847,593 (applied as an evidentiary reference).

There is no overlapping subject matter between the claims of the '189 patent and the present claims, since the present claims require an -OY substituent, where Y is C<sub>1</sub>-C<sub>6</sub> alkyl, and the '189 patent requires -OH.



The '593 application is not prior art<sup>1</sup> and cannot be used to establish a motivation or suggestion to replace the –OH group of the '189 patent with the –OY substituent of the present claims, nor establish a reasonable expectation of success for such a substitution. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure, *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

Furthermore, as shown in Tables 1, 2 and 3 of the present application the substitution of –OY for –OH produced significant differences in chemical properties of the otherwise identical compounds 1 (–OY) and A (hydroxy) or compounds 2 (–OY) and B (hydroxy) showing that –OY substituted compounds are not equivalents of those covered by the prior patent. Therefore, this rejection cannot be sustained.

#### Obviousness-type Double Patenting

Claims 1 and 7-25 were rejected under the judicially-created doctrine of obviousness type double patenting over claims 1-8 of U.S. Patent No. 7,307,077, in view of copending U.S. Application No. 11/847,593 (applied as an evidentiary reference).

There is no overlapping subject matter between the claims of the '077 patent and the present claims, since the present claims **require an –OY substituent**, where Y is C<sub>1</sub>-C<sub>6</sub> alkyl, and the '077 patent **requires hydrogen, amino or –OH**. Moreover, the '077 does not specify the 4-position on the ring.

The '593 application is not prior art<sup>2</sup> and cannot be used to establish a motivation or suggestion to replace the –OH group of the '077 patent with the –OY substituent of the

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<sup>1</sup> The '593 application is a continuation of PCT/JP06/04937, filed March 13, 2006; the pending application is a national-stage filing of PCT/JP05/06111, filed March 30, 2005.

<sup>2</sup> The '593 application is a continuation of PCT/JP06/04937, filed March 13, 2006; the pending application is a national-stage filing of PCT/JP05/06111, filed March 30, 2005.



present claims, nor establish a reasonable expectation of success for such a substitution . The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure, *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

Furthermore, even if prior art had been cited suggesting such a substitution, as shown in Tables 1, 2 and 3 of the present application the substitution of –OY for –OH produced significant differences in chemical properties of the otherwise identical compounds 1 (-OY) and A (hydroxy) or compounds 2 (-OY) and B (hydroxy) showing that –OY substituted compounds are not equivalents of those covered by the prior patent. Therefore, this rejection cannot be sustained.

Rejection—35 U.S.C. §112, first paragraph

Claims 21-25 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate enablement. The Examiner agrees that these claims are enabled for treating human colon cancer, but indicates that as directed to treatment of other human tumors they are not enabled.

Presumption of Enablement supported by experimental data of record:

A specification which discloses how to make and use a claimed invention is presumed to comply with the first paragraph of 35 U.S.C. §112, unless there is a reason to doubt the objective truth of the specification, *In re Marzocchi*, 169 USPQ 367 (CCPA, 1971). The Examiner has not provided any reason to doubt that the compound of formula (I) treats different types of tumor cells. The specification discloses that the compounds used in the claimed methods of treatment inhibits the growth of human colon cancer, human lung cancer, human breast cancer, and human prostate cancer cells *in vitro* (see the paragraph bridging pages 19-20 of the specification). Moreover, the specification demonstrates the claimed methods inhibit the growth of colon cancer cells *in vivo* (see the *in vivo* antitumor Test 2 on



pages 17-19 of the specification). If the claimed methods inhibit the growth of different types of tumor cells *in vitro* and the Applicants have demonstrated a correlation between *in vitro* inhibition of the growth of human colon cancer cells and inhibition of human cancer cell growth *in vivo*. The Examiner's attention is directed to MPEP 2164.02:

Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

[B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

In the present situation, based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity as shown by the results for human colon cancer cells. This correlation demonstrates that the compound of formula (I) used in the claimed methods is bioavailable and can be administered in an amount effective to reduce the growth of cancer cells *in vivo*. The Examiner has not provided any reasons for doubting that when administered *in vivo* that the same compound would not inhibit the growth of other types of cancer cells as it does *in vitro*. Thus, while the Examiner cites particular case law throughout the rejection with regard to scope of enablement, he provides no technical or scientific reasoning based on the evidence as a whole sufficient to rebut the clear factual showings in the specification that the compound of formula (I) can inhibit the growth of numerous different types of tumor cells.

Another reason why one of skill in the art at the time of invention would have accepted the *in vitro* results as being predictive of similar effects *in vivo* (aside from the correlation for colon cancer cells shown by the Applicants), is that other compounds having a similar core structure were known to act *in vivo* on a number of different types of cancer



cells, see e.g., Yaguchi, et al., J. Nat. Cancer Inst. 98:545 (2006). This reference shows that compounds having a similar core structure to formula (I), see Fig. 1 on page 548, act *in vivo* on a variety of different cancer cells in animal, human-xenograft models of non-small-cell lung cancer, prostate cancer, and colon cancer (bottom of col. 2, p. 552). Yaguchi also identifies a molecular target of a compound (ZSTK474) sharing this core structure with formula (I)(see page 548, col. 2) and reviews the mechanism of action for this type of triazine compound. The experimental results and teachings of Yaguchi thus further support a broader scope of enablement of the invention with respect to activity on other types of cancer cells.

What was not known in the prior art and what the inventors have discovered, is that substitution of an alkoxy substituent at position 4 of the benzimidazole ring in this class of compounds significantly improved the pharmacokinetics of this type of alkylating anti-tumor compound and expanded its anti-cancer activities.

No undue experimentation:

Assuming *arguendo* that there were some reason to doubt that the claimed heterocyclic compounds would exert the same broad spectrum of anti-tumor or anti-cancer activity of other similar compounds, this still would not render the claims not enabled, since no undue experimentation would have been required to determine which types of cancers could be treated using the claimed methods. So long as so long as one of ordinary skill in the art can distinguish between operative and inoperative embodiments without "undue experimentation," then one of skill in the art can "make and use" the invention in accordance with 35 U.S.C. §112, first paragraph, see *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984) (holding that claim encompassing inoperative



embodiments may be enabled if one of ordinary skill can distinguish inoperative embodiments without undue experimentation).

Even a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed, *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

Based on the application of the factors described by *Wands*, no undue experimentation would be required to practice the invention for the following reasons:

(A) the breadth of the present method of treatment claims limits them to a narrow structurally-defined genus of chemical compounds, as described by claim 1.

(B) The nature of the invention involves inhibiting cancer cell growth and the mechanics of administering the recited compounds were straightforward and well within the skill of those in the art.

(C) The state of the prior art shows that methods for inhibiting tumor cell growth using s-triazine and pyrimidine derivatives were well-known and conventional.

(D) The level of ordinary skill in the molecular biological arts was high, generally Ph.D or post-doctoral level.

(E) The level of predictability in the art is high, since parental s-triazine and pyrimidine compounds and methods for administering them to treat cancer as well as for evaluating their efficacy were well-known and are exemplified in the specification.

(F) and (G) The amount of direction provided by the present inventors is high and the claimed method is exemplified.

Accordingly, for all of these reasons, this rejection cannot be sustained.



Application No. 10/594,994  
Reply to Office Action of February 24, 2010

Rejection—35 U.S.C. §112, second paragraph

Claims 22-25 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. This rejection is moot in view of the amendments above.

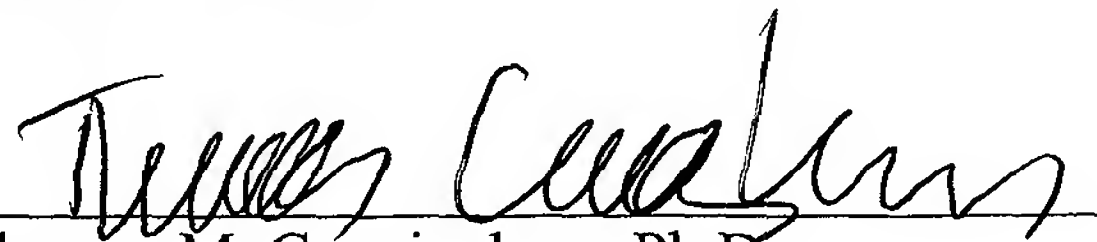


Conclusion

This application presents allowable subject matter and the Examiner is respectfully requested to pass it to issue. The Examiner is kindly invited to contact the undersigned should a further discussion of the issues or claims be helpful.

Respectfully submitted,

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